Intranasal bevacizumab in the treatment of HHT – related epistaxis: a systematic review*

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Abstract

Background: Hereditary haemorrhagic telangiectasia (HHT) remains a difficult disease for the ENT specialist to manage. Affected patients often report recurrent epistaxis as the most debilitating symptom. The pathogenesis of the disease is due to genetic mutations affecting angiogenesis. For this reason, the anti-angiogenic therapy bevacizumab has gained popularity in the local treatment of epistaxis in patients with HHT.

Objective: A systematic review of the efficacy of bevacizumab in local treatment of epistaxis in patients with HHT based on epistaxis duration, frequency, severity and impact on quality of life.

Methods: A systematic search was performed using the PubMed, MEDLINE and EMBASE databases. The Preferred Items for Systematic Reviews and Meta-Analyses guidelines were followed. Studies that measured the efficacy of intranasal bevacizumab treatment of epistaxis in patients with HHT were included for qualitative analysis.

Results: Thirteen studies (four randomised controlled trials, three prospective studies, three retrospective studies, one case series and two case reports) with a total of 357 patients were included. Local administration (either by submucosal injection or topically) did not have a significant impact on epistaxis duration, frequency, severity or quality of life compared to placebo or other local treatments.

Conclusions: The available evidence suggests that intranasal bevacizumab treatment does not have a significant effect on epistaxis in patients with HHT. There are several limitations that require further investigation to confidently rule out local bevacizumab as an effective therapy in HHT related epistaxis.

Key words: Hereditary haemorrhagic telangiectasia, bevacizumab, Avastin, epistaxis, vascular endothelial growth factor

Introduction

Hereditary haemorrhagic telangiectasia (HHT, also known euphemistically as Osler-Weber-Rendu syndrome) remains a difficult disease for the ENT specialist to manage. HHT is an autosomal dominant vascular disease with a reported prevalence of 1 in 5,000 to 9,000, dependent on geographical location¹². The disease is characterised by arteriovenous malformations (AVMs) in visceral and/or mucocutaneous tissues¹⁰. However, often the most debilitating symptom is persistent and severe epistaxis derived from telangiectasias within the nasal mucosa. The treatment spectrum ranges from local application of anti-angiogenic agents, nasal packing and cauterisation through to the definitive management being nasal closure¹⁴.⁷
To date, multiple mutations in two genes have been well described in the pathogenesis of HHT. These are in the ENG gene on chromosome 9, which encodes for the protein endoglin, and the ACVR1 gene on chromosome 12, which codes for activin receptor – like kinase 1 (ALK1)[8,9]. Several hundred mutations have been described in these two genes alone, causing HHT1 and HHT2 respectively[8]. A third gene, MADH4 on chromosome 18, codes for SMAD4 protein; mutations in this gene cause a juvenile polyposis/HHT overlap syndrome that accounts for less than 2% of HHT[10]. Further gene loci have recently been identified, causing HHT3 and HHT4 subtypes.

The proteins encoded by these genes mediate signalling in many cellular pathways including angiogenesis. In HHT, mutations can lead to elevated levels of transforming growth factor (TGF) – beta and vascular endothelial growth factor (VEGF) that when overexpressed have been linked to abnormal, immature and disorganised vascular growth prone to constant remodelling and rupture[11,12]. With this in mind, anti – angiogenic agents have become of significant therapeutic interest in the treatment of HHT.

Over the past decade, bevacizumab (Avastin, Genentech Inc, San Francisco, CA, USA) has gained popularity in the treatment of HHT[5,12]. Bevacizumab is a selective recombinant human antibody against VEGF – A isomers. The drug, originally licenced for oncological practice[13], has recently been used to control intraocular neovascular disorders[14]. It has also become first-line treatment for symptomatic hepatic AVMs in HHT, reducing the need for liver transplantation in these patients[15]. Based on this success, several studies have analysed the effect of bevacizumab on other HHT outcomes including epistaxis[16-29]. Despite initial promising results, it remains unclear whether the agent provides any true benefit in epistaxis outcomes in these patients. To complicate matters further, there are no standardised dosing regimes, including preferred route, dose strength and duration/frequency[20]. This systematic review aims to assess the relevant current literature regarding the efficacy of intranasal application of bevacizumab in the management of HHT-related epistaxis in an attempt to answer some of these questions.

Methods
Eligibility criteria
Inclusion and exclusion criteria were predefined. Inclusion criteria included English language, human studies that analysed the efficacy of treatment with intranasal bevacizumab (see types of interventions) in HHT-related epistaxis. Case reports or series, letters to the editor and abstracts were included if they held adequate data. Non – English, review articles and any in vitro or animal studies were excluded from this review.

Types of interventions
Intranasal bevacizumab may be administered by nebulisation, spray or submucosal injection within the nose.

Types of outcome measures
Primary
Efficacy of epistaxis management with intranasal bevacizumab in patients with HHT as defined by:
- Subjective measurements
  - Symptom scores (visual analogue scales; epistaxis severity score (EpSS); intensity, frequency and transfusion score (IFT))
  - Quality of life questionnaires (36 – Item Short Form Health Survey (SF – 36))
- Objective measurements
  - Haemoglobin and ferritin levels

Secondary
- Surrogate outcome
  - Number of hospital admissions
  - Transfusion requirements
- Adverse events associated with treatment

Search strategy
A systematic search was performed by using the PubMed, MEDLINE, and EMBASE databases. The PubMed database was searched from inception until December 12, 2016; EMBASE was searched from 1974 until December 12, 2016, and MEDLINE was searched from 1946 to December 12, 2016 by using Ovid SP. Bibliographies of studies selected for full – text analysis were reviewed for any additional missing studies. An electronic search strategy was designed to identify all studies concerned with the efficacy of topical administration of bevacizumab in HHT-related epistaxis.

Data collection and analysis
Two unblinded reviewers (P.S. and J.R.) reviewed the titles and abstracts, read full – text articles and evaluated them against the inclusion criteria. Studies that met the inclusion criteria had the relevant data extracted using a standardised data form. The Preferred Reporting Items for Systematic Reviews and Meta – Analyses (PRISMA) flow diagram for study selection is shown in Figure 1.

The review authors (P.S. and J.R.) conducted the data extraction and assessed the quality of the method used in each included trial. Considered factors were:
- Number of participants
- Age of participants
- Sociodemographic data
- Characteristics of trial (e.g. method of randomisation, blinding, the use of intention – to – treat analysis)
Intranasal bevacizumab in HHT

review (four randomised controlled trials\cite{16-19}, three prospective cohort studies\cite{20-22}, three retrospective studies\cite{23-25}, one case series\cite{26} and two case reports\cite{27,28}, totalling 357 patients (see Table 1). However, this number may be inaccurate with two controlled trials\cite{17,18} and two cohort studies\cite{21,23} coming from two institutions, increasing the likelihood that patients were included in one or more studies.

In the four controlled trials\cite{16-19}, 113 patients received topical bevacizumab spray, 9 intranasal submucosal injections and 119 received placebo or non–bevacizumab treatment. From the prospective data, 6 patients received topical bevacizumab alone, 10 patients received local submucosal injections whilst 17 patients received combination therapy\cite{20-22}. In retrospective studies, 17 patients received topical bevacizumab and 31 patients received local submucosal injections whilst 5 received combination therapy\cite{23-25}.

Study objectives
All thirteen studies assessed the efficacy of intranasal bevacizumab on epistaxis in HHT. Three controlled trials assessed the efficacy of bevacizumab as a primary objective\cite{16,17,19}. One trial studied efficacy as a secondary objective; the primary objective was to investigate the tolerance of incremental doses of intranasal bevacizumab in HHT\cite{18}. All other included papers primarily analysed the efficacy of bevacizumab in HHT, with secondary objectives including the tolerance and safety of administration of intranasal bevacizumab and overall effect on quality of life.

Interventions
Bevacizumab was administered either submucosally as an injection or topically as a nasal spray or nebuliser (Table 1). Five studies analysed administration of bevacizumab topically as a stand-alone treatment\cite{16-18,20,26}. The method of administration varied, either being nebulised (every 30 minutes for 2 hours, or until completion of a given dose)\cite{17,18,20,26} or administered as a spray (twice daily)\cite{19}. The dosing interval also varied as either a daily treatment for one week\cite{16}, at three fourteen day intervals\cite{27}, monthly\cite{26} or as a one off treatment\cite{18,20}. Total dosage ranged from 12.5mg to 100mg per treatment cycle. Duration of follow up ranged from 2.8 to 6 months.

Six studies analysed the efficacy of submucosal injection of bevacizumab\cite{19,22-24,26}. In cohort studies, submucosal injection of bevacizumab was either as a one off single therapy\cite{19,22} or in conjunction with laser treatment\cite{23-25}. The total dose of bevacizumab administered submucosally varied between 3.75mg, 50mg and 100mg per injection. Duration of follow up ranged from 9.5 weeks to 1 year.

Three studies analysed combination therapy\cite{21,23,27}. The three studies that investigated dual submucosal and topical therapy

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**RESULTS**

Search
A total of 125 references were identified by the search. Of these, 79 studies were removed in first–level screening (eg removal of duplicates, clearly irrelevant references and non–English studies) leaving 46 references for consideration. A further 33 publications were excluded because they did not meet the inclusion criteria. Thirteen articles\cite{16-20} were included in the final
utilised the same regime with 100mg of bevacizumab injected submucosally plus 50mg to 100mg administered topically for non-respondents(21,23,27). Follow up ranged from 4.1 to 12 months.

Outcomes

**Effect on epistaxis severity**

Epistaxis severity was directly measured using mean duration and frequency, via scoring systems, or through surrogate markers (eg biological parameters or transfusion rates) (Table 2). All four randomised controlled trials analysed mean duration of epistaxis episodes following bevacizumab treatment; none reported a significant difference compared to placebo or other therapeutic agents including estriol and tranexamic acid at three and six months, regardless of bevacizumab dosage(16-19).

Three randomised trials were unable to show a significant change in frequency of epistaxis episodes following treatment with bevacizumab(16-18). One retrospective study showed a significant decrease in frequency of epistaxis in patients injected with bevacizumab as an adjunct to laser therapy at one month post intervention(25).

Several different scoring systems were used to quantify epistaxis outcomes including the epistaxis severity score (EpSS)(16,19-24), visual analogue scores (VAS) of epistaxis severity(19), intensity frequency transfusion score (IFT)(22) or non-standardised study-specific scores(25). Two controlled trials specifically analysed the EpSS(16,19). Whitehead et al showed a significant improvement in EpSS at 3 months for all treatments including placebo, but with no benefit from bevacizumab over other treatments(16). Riss et al were unable to show a significant change in the average daily epistaxis VAS.

Contrary to this, several prospective and retrospective studies showed a significant improvement in EpSS scores at three months following bevacizumab treatment(20-24). In one prospective review this improvement was limited only to patients presenting with mild pre-treatment EpSS scores(20). One prospective

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Route</th>
<th>Dose (total)</th>
<th>Adjunct therapy</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitehead et al. 2016(16)</td>
<td>RCT</td>
<td>Topical</td>
<td>Bevacizumab nasal spray BD for 1 week (28mg) then normal saline BD for 12 weeks</td>
<td>Nil serious related</td>
<td></td>
</tr>
<tr>
<td>Dupuis - Girod et al. 2016(17)</td>
<td>RCT</td>
<td>Topical</td>
<td>Bevacizumab (25mg/ml) nasal spray every 14/7 for 3 doses as 25mg, 50mg or 75mg per treatment dose (75mg, 150mg, 225mg)</td>
<td>Nil serious related</td>
<td></td>
</tr>
<tr>
<td>Dupuis - Girod et al. 2014(18)</td>
<td>RCT</td>
<td>Topical</td>
<td>Bevacizumab (25mg/ml) nasal spray for one dose (12.5mg, 25mg, 50mg, 75mg or 100mg)</td>
<td>Hypertension, rhinopharyngitis and cephalgia</td>
<td></td>
</tr>
<tr>
<td>Riss et al. 2014(19)</td>
<td>RCT</td>
<td>Injection</td>
<td>Bevacizumab (10mg/ml) 5ml injected into each nostril (50mg)</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Guldmann et al. 2012(20)</td>
<td>Prospective review</td>
<td>Topical</td>
<td>Bevacizumab (25mg/ml) nasal spray as single dose (50mg) Option to have second dose 2/12 post treatment</td>
<td>Nil serious related</td>
<td></td>
</tr>
<tr>
<td>Karnezis et al. 2012(21)</td>
<td>Prospective review</td>
<td>Injection/ topical</td>
<td>Bevacizumab (25mg/ml) injected (100mg) Option to have additional bevacizumab nasal spray (100mg)</td>
<td>Nil serious related</td>
<td></td>
</tr>
<tr>
<td>Dheyaaldeen et al. 2012(22)</td>
<td>Prospective pilot study</td>
<td>Injection</td>
<td>Bevacizumab (25mg/ml) injected (50mg)</td>
<td>Nil serious related</td>
<td></td>
</tr>
<tr>
<td>Karnezis et al. 2011(23)</td>
<td>Retrospective review</td>
<td>Injection/ topical</td>
<td>Bevacizumab nasal spray (50 - 100mg) Option to have additional 1 -2 additional courses Bevacizumab injected (100mg)</td>
<td>KTP laser Nil serious related</td>
<td></td>
</tr>
<tr>
<td>Rohrmeir et al. 2011(24)</td>
<td>Retrospective review</td>
<td>Injection</td>
<td>Bevacizumab 3.75mg/ml injected (0.3mg - 3.75mg) Nd:YAG laser</td>
<td>Nil serious related</td>
<td></td>
</tr>
<tr>
<td>Simonds et al. 2009(25)</td>
<td>Retrospective review</td>
<td>Injection</td>
<td>Bevacizumab injected (100mg) KTP laser</td>
<td>Septal perforation x 4</td>
<td></td>
</tr>
<tr>
<td>Alderman, 2013(26)</td>
<td>Case series</td>
<td>Topical</td>
<td>Bevacizumab (25mg/ml) nebulised (100mg) every month for 3/12</td>
<td>Pulsed dye laser Nil serious related</td>
<td></td>
</tr>
<tr>
<td>Davidson 2009(27)</td>
<td>Case report</td>
<td>Injection</td>
<td>Bevacizumab injected (100mg), then bevacizumab (10mg/ml) nasal spray BD for 2/52 (28mg), then bevacizumab (25mg/ml) nasal spray as one dose (25mg)</td>
<td>Diode laser (810nm units) Nil serious related</td>
<td></td>
</tr>
<tr>
<td>Marglani 2013(28)</td>
<td>Case report</td>
<td>Injection</td>
<td>Bevacizumab injected (100mg)</td>
<td>Nil serious related</td>
<td></td>
</tr>
</tbody>
</table>
Intranasal bevacizumab in HHT

Pilot study of submucosal bevacizumab injection recorded the IFT grading system in addition to the EpSS, and showed a significant improvement in bleeding burden after a mean follow up of 9.5 weeks (22).

Five studies analysed biological parameters, namely serum haemoglobin and ferritin (16-18, 22, 24), as surrogate markers for epistaxis burden. Three randomised controlled trials were unable to show a significant improvement in haemoglobin or ferritin levels following bevacizumab treatment (16-18). Contrary to this, one smaller prospective and one retrospective study did show a significant improvement in haemoglobin levels at 9.5 weeks post-intervention (22, 24).

Blood transfusions were used as an independent outcome measurement in five studies, including three randomised controlled trials (16-18, 24, 25). None showed a significant reduction in the number of patients requiring blood transfusions, nor a reduction in individual transfusion requirements, at three or six months. However, two reported a reduction in blood transfusion rates over one year post-bevacizumab treatment (24, 25), although this decline was only statistically significant in one study (24).

Quality of Life
Two studies used the standardised 36 item short form questionnaire (SF – 36) to assess quality of life post-bevacizumab treatment (17, 22), whilst others used their own non-standardised

Table 2. The effect of bevacizumab on epistaxis outcomes.

<table>
<thead>
<tr>
<th>Author</th>
<th>Epistaxis duration</th>
<th>Epistaxis frequency</th>
<th>Surrogate markers</th>
<th>Duration of follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitehead et al. 2016 (16)</td>
<td>Nil effect (P=0.47)</td>
<td>Significant decrease (P&lt;0.01)</td>
<td>Nil effect on Hb (P=0.43)</td>
<td>24 weeks (weekly for 5-12/52 and then at 12/52)</td>
</tr>
<tr>
<td>Dupuis - Girod et al. 2016 (17)</td>
<td>Nil effect regardless of dosing: 25mg (P=0.71), 50mg (P=0.72) or 75mg (P=0.67)</td>
<td>Nil effect on ferritin (P=0.55)</td>
<td>Nil effect on Hb (P=0.68)</td>
<td>6 months (twice at 3/12 and 6/12 post treatment)</td>
</tr>
<tr>
<td>Dupuis - Girod et al. 2014 (18)</td>
<td>Nil effect (P=0.40)</td>
<td>Nil effect on ferritin requirements</td>
<td>Nil effect on Hb</td>
<td>3 months (day 14, 30 and 90 post treatment)</td>
</tr>
<tr>
<td>Riss et al. 2014 (19)</td>
<td>Nil effect (P=0.86)</td>
<td></td>
<td></td>
<td>12 weeks (every 4/52 for 12/52 post treatment)</td>
</tr>
<tr>
<td>Guldmann et al. 2012 (20)</td>
<td>Significant decrease in mild cases (EpSS&lt;7) at two months (P=0.015); not significant at three months or in severe cases (EpSS&gt;7)</td>
<td>Nil effect on ferritin (P=0.68)</td>
<td>Nil effect on ferritin requirements (P=0.39)</td>
<td>2.8 months (mean); day 10 post treatment, and then every 1/2 for 3/12</td>
</tr>
<tr>
<td>Karnezis et al. 2012 (21)</td>
<td>Nil effect (P=0.001)</td>
<td></td>
<td></td>
<td>12 months (every 1/2 for duration of study)</td>
</tr>
<tr>
<td>Dheyauldeen et al. 2012 (22)</td>
<td>Significant decrease (P&lt;0.001)</td>
<td>Significant increase in Hb (P=0.01)</td>
<td></td>
<td>9.5 weeks (mean); at 1/2 (by phone)</td>
</tr>
<tr>
<td>Karnezis et al. 2011 (23)</td>
<td>Significant decrease (P&lt;0.0005)</td>
<td>Significant increase in ferritin requirements (P&lt;0.04)</td>
<td></td>
<td>4.1 months (mean); (3.4/12 for topical, 5/12 for submucosal, 4.7/12 months for subdural)</td>
</tr>
<tr>
<td>Rohrmeier et al. 2011 (24)</td>
<td>Significant decrease (P=0.005)</td>
<td>Significant increase in Hb (P=0.011)</td>
<td></td>
<td>Not recorded</td>
</tr>
<tr>
<td>Simonds et al. 2009 (25)</td>
<td>Significant decrease in transfusion requirements (P=0.04)</td>
<td></td>
<td></td>
<td>1 year (phone interviews at 1/2 and 12/12 post treatment)</td>
</tr>
<tr>
<td>Alderman et al. 2013 (26)</td>
<td>Reduced daily minutes (35 - 4)</td>
<td>No transfusions post treatment</td>
<td></td>
<td>5 months</td>
</tr>
<tr>
<td>Davidson et al. 2009 (27)</td>
<td>Reduced bleeding</td>
<td>Decrease (4.9 - 1.07)</td>
<td></td>
<td>10.5 months</td>
</tr>
<tr>
<td>Marglani et al. 2013 (28)</td>
<td>Reduced frequency</td>
<td>Increase in Hb (7.8mg/dl - 9.3mg/dl)</td>
<td></td>
<td>10 months</td>
</tr>
</tbody>
</table>

### Quality of Life

Two studies used the standardised 36 item short form questionnaire (SF – 36) to assess quality of life post-bevacizumab treatment (17, 22), whilst others used their own non-standardised methods.
scoring systems. In the largest and most well-powered study, Dupuis – Girod et al found no difference in quality of life six months after bevacizumab treatment, validating previous findings. One prospective study used several other quality of life questionnaires that showed trending improvements with bevacizumab although these were not statistically significant. Two retrospective studies that analysed quality of life found a significant improvement in a majority of patients using non-standardised scoring systems, although these results were not quantified or analysed further.

Side effect profile

Eight studies documented general adverse effects of treatment. Of these, three studies noted adverse effects that were potentially linked to bevacizumab treatment. These included two cases of hypertension (one requiring further treatment and physician input), as well as rhinopharyngitis, cephalgia and septal perforation. The four cases of septal perforation forced the authors to change their protocol for submucosal injection of bevacizumab.

Discussion

Despite initial promising results, the available data suggests that locally administered bevacizumab may not provide the expected therapeutic benefits in HHT patients with epistaxis. Primary outcome measurements for epistaxis severity were relatively homogenous amongst the included studies with most reporting either mean duration and/or frequency of epistaxis episodes, or using the validated epistaxis severity score (EpSS). All four randomised controlled trials were unable to show any significant effect of bevacizumab on the mean duration of frequency of epistaxis or any significant improvement in the EpSS after intranasal bevacizumab treatment, contradicting the findings of several earlier, smaller cohort studies. One explanation for this may be the source of the data. Two case series were derived from the same centre, as were two controlled trials, and it is likely that patients were included in multiple data sets, thus minimising the impact of their findings. Regardless of this, all included studies faced limitations of subjective reporting of primary outcome measures. Epistaxis reporting relied on the patient either filling out study specific grids, diaries or other recording templates, or retrospective mental recollection that is prone to error. Many studies were limited by short follow-up periods of three months or less. This makes extracting baseline epistaxis data difficult, and may also underestimate treatment response. Furthermore, several different scoring systems were used, preventing meta-analysis. The most widely used epistaxis severity scoring system in the literature is the EpSS that has itself been criticised for interpatient variability, ambiguous questioning and sociodemographic bias (eg questions that assume access to health care is readily available). Even quantitative data such as biological markers may not be fully defensible as protocols or reasons for transfusing or initiating other treatment may vary between hospitals and individual patients based on clinical parameters.

Some authors have attributed the poor therapeutic response to bevacizumab’s biological properties. Bevacizumab has a large molecular weight that may hinder its bioavailability when locally administered, especially in the setting of additional barriers to the nasal mucosa such as mucus and crusting. No studies comprehensively accounted for patients’ previous surgeries that may have influenced drug absorption. Despite this, it has been shown in ex vivo porcine nasal mucosal models that the majority of delivered bevacizumab could be retrieved either within or across the mucosal barrier suggesting that the local bioavailability of the drug is good. In further support of local administration, diluted bevacizumab has been deemed stable during prolonged refrigerated storage in polyethylene bottles and this would therefore not be responsible for the hypothesised poor pharmacokinetics and/or bioavailability of the drug. To truly validate this bioavailability hypothesis would require human tissue that would likely result in worsening of the epistaxis burden in patients with an already morbid baseline.

There is no evidence that the use of topical or local bevacizumab significantly improved the patients’ quality of life, although there were some trends towards this. As noted previously, this data is difficult to interpret due to its subjective nature. In patients with HHT, questions pertaining to quality of life are especially problematic as disease related characteristics (e.g. duration of illness, type of gene mutation, and presence of other HHT manifestations) may have a significant impact on the quality of life beyond the scope of the treatment of epistaxis. The SF – 36, used by two studies in this review, has been used previously to assess the effect of treatment of HHT-related epistaxis with conflicting results. There have been attempts to construct tools that are more specific in measuring epistaxis related outcomes, although the current literature shows no consensus on how to best analyse quality of life in this patient population.

The available data suggests that bevacizumab is well tolerated and can be safely administered as a local agent. The most significant known adverse events associated with the systemic administration of bevacizumab include venous thrombosis, gastrointestinal perforation, haemorrhage, proteinuria and wound complications, of which none were reported with topical administration. The most notable local adverse effect was septal perforation associated with submucosal injection of bevacizumab. This has been validated by a second study not
included in this review due to irrelevant outcome measures\(^\text{\scriptsize{36}}\). The recommendation of the authors was to always consider the risk of septal perforation when providing the treatment, and inject only into the lateral walls and non-cartilaginous septum to minimise this risk\(^\text{\scriptsize{25,36}}\). This technique in itself may adversely affect the results seen with submucosal bevacizumab injection, as the mucosa overlying the cartilaginous septum is often a predominant site of bleeding in HHT; not injecting in this area is therefore likely to be less effective.

Many of the included studies lacked adequate power to draw definitive conclusions, with patient cohorts ranging from 3 to 121\(^\text{\scriptsize{16,17,26}}\). The largest of the controlled trials\(^\text{\scriptsize{16}}\) included 29 patients randomised to receive topical bevacizumab that differed in dosing regime compared to previous controlled trials\(^\text{\scriptsize{17-19}}\). The heterogeneity of administration routes, dosing regimes, concurrent therapies and follow up protocols jeopardise meaningful data analysis and hinder drawing definitive conclusions from the current data. Both topical and submucosal dosaging was variable. The most common topical dosing regime was 25mg/ml (0.1ml/spray) every 30 minutes over two hours\(^\text{\scriptsize{17,18}}\). Yet even this differed between studies as either a one off treatment\(^\text{\scriptsize{16}}\), or given in multiple fortnightly intervals\(^\text{\scriptsize{17}}\). Similarly, submucosal injection dosing varied from 0.3mg\(^\text{\scriptsize{24}}\) to 100mg\(^\text{\scriptsize{21,23,25}}\), as did the presence of additional adjunctive therapy either with laser or topical bevacizumab\(^\text{\scriptsize{21,22,23}}\). To address this variability, a dosing regime based on the pretreatment EpSS has been proposed, whereby a pretreatment EpSS greater than five may qualify a patient for dual therapy (submucosal and topical) whilst that less than five may warrant only topical\(^\text{\scriptsize{21,23}}\). This defined cut off remains somewhat arbitrary and unsurprisingly there remain no formal or standardised guidelines for the dosing regime of intranasal bevacizumab in HHT.

**Conclusions**

Recent high quality data from controlled trials suggests that local bevacizumab therapy may not be effective in the treatment of HHT – related epistaxis compared to placebo or other treatments (estriol or tranexamic acid), contradicting earlier reports. This evidence is based on primary outcome measurements of mean duration and frequency of bleeding episodes, subjective severity scoring systems (namely the EpSS), surrogate measurements of bleeding including biological parameters and blood transfusions, and quality of life following bevacizumab treatment. Although several randomised controlled trials exist, similar sample populations and limited power compounded by heterogeneous treatment regimes constrain their findings\(^\text{\scriptsize{16-18}}\). To confidently exclude bevacizumab as a local treatment in HHT-related epistaxis, larger longitudinal or randomised and prospective trials with standardised dosaging regimes are required.

**Authorship contribution**

PS: Collation, analysis and synthesis of systematic review.
JR: Collation, analysis and editing of systematic review.

**Conflict of interest**

None.

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